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(54) Title: PROCESS FOR THE ENHANCEMENT OF THE DESICCATING CAPACITY OF POLYMERS

(57) Abstract

A process for the enhancement of the desiccating capacity of a desiccant polymer characterised in that it includes the step of exposing the said desiccant polymer to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules.

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PROCESS FOR THE ENHANCEMENT OF THE DESICCATING CAPACITY OF POLYMERS

This invention relates to a process for the enhancement of the desiccating capacity of polymers, particularly the enhancement of the desiccant capacity of 5 desiccant polymers.

Desiccant polymers are polymers which exercise a desiccating effect on their environment by absorbing water from the surrounding atmosphere. Desiccant polymers may be an inherently desiccant polymeric material, such as hydrophilic polymers or may be of the type comprising a polymeric matrix in which is dispersed a desiccant 10 material.

Inherently desiccant polymers include the known water-absorbent hydrophilic polymers used for the manufacture of contact lenses, artificial cartilages and other bodily implants etc.

Desiccant polymers of the type comprising a polymeric matrix in which is 15 dispersed a desiccant material are disclosed *inter alia* in WO 96/04189, which discloses desiccant polymers which comprise an elastomeric matrix, such as a halobutyl rubber, in which are dispersed particles of an inorganic desiccant such as molecular sieve or calcium oxide. WO 96/04189 also discloses the use of solid bodies made of such desiccant polymers to desiccate moisture sensitive materials such as 20 pharmaceutical substances, e.g drug compounds and lyophilised products, in containers by exposing the atmosphere in such a container to the body. In particular WO 96/04189 discloses vials containing such substances, sealed with an elastomeric stopper having a puncturable region such as a thin part of the stopper wall through which a hypodermic needle may be inserted, in which the stopper is made of such a 25 desiccant polymer.

A problem with such desiccant polymers is that they may absorb quantities of water, particularly as water vapour, prior to their use, and this absorbed water can reduce their desiccant capacity. For example vial stoppers may absorb water from the atmosphere or during the water washing operations used during their manufacture. 30 Inorganic desiccants such as molecular sieve or calcium oxide generally require high temperatures, typically several hundred °C to drive off absorbed water, and such temperatures would destroy the polymer matrix.

It is an object of this invention to provide a process by means of which this problem might be overcome.

35 According to this invention, a process for the enhancement of the desiccating capacity of a desiccant polymer includes the step of exposing the said desiccant polymer to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules.

It has also been found that exposing polymers which are generally considered to be non-desiccant polymers to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules can enhance their desiccating capacity, even if they contain no desiccant material dispersed within their bulk.

5 Therefore in a second aspect of this invention a process for enhancing the desiccating capacity of a polymer, or of imparting a desiccating capacity to a polymer includes the step of exposing the said polymer to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules.

10 The enhancement of the desiccating capacity, or impartation of desiccating capacity by the process of this invention may be part of a process in which the polymer, whether a desiccant polymer or otherwise, is activated, re-activated or regenerated. It is believed that the enhancement or impartation of desiccant capacity occurs as a result of preferential absorption of the radiation by water molecules in the polymer and/or absorbed by the desiccant material, so that water molecules are caused 15 to be heated by the radiation and thus driven out of the polymer. However the invention is not limited by any particular theory of operation.

The desiccant polymer may be an inherently desiccant polymeric material, such as hydrophilic polymers, or may be of the type comprising a polymeric matrix in which is dispersed a desiccant material.

20 Suitable hydrophilic polymers include hydrogel polymers, such as polymers which comprise hydroxy alkyl methacrylates, for example 2-hydroxyethyl methacrylate. Other suitable desiccant polymer include the homologous esters of the glycol monomethacrylate series such as diethylene glycol monomethacrylate and tetraethylene glycol monomethacrylate; slightly cross-linked, for example with a dimethacrylate of a glycol, copolymers of the higher glycol monomethacrylates and 2-hydroxyethyl methacrylate, acrylamide hydrogels and 2-hydroxyethyl methacrylate-vinylpyrrolidinone copolymers. Such polymers may be cross linked for example with ethylene dimethacrylate and/or 1,1,1- trimethyl-propane trimethacrylate. Other suitable polymers include water-insoluble methacrylates copolymerised with 2-hydroxyethyl 25 methacrylate. Poly (2-hydroxyethyl methacrylate) polymers can for example absorb up to 40% w:w of water. Copolymers of 2-hydroxyethyl methacrylate with a small amount of a dimethacrylate, some methyl or other alkyl methacrylate and some methacrylic acid, which can be converted to their alkali salts, can absorb at least 45% w:w of water. Copolymers of 2-hydroxyethyl methacrylate may for example also be 30 copolymerised with n-pentyl methacrylate, vinyl propionate, vinyl acetate, isobutyl and cyclohexyl methacrylate, to produce a suitable desiccant polymer. Copolymers of 2-hydroxyethyl methacrylate with vinylpyrrolidinones, such as 1-vinyl-2-pyrrolidinone, and which may be cross linked with ethylene glycol dimethacrylate, can produce 35 hydrogels with a higher degree of hydration, suitable as desiccant polymers. Other

suitable hydrogel polymers include hydroxyethyl methacrylate - N,N-dimethylacrylamide copolymers, hydroxyethyl methacrylate - N-vinyl pyrrolidone copolymers, hydroxyethyl methacrylate - acryloyl morpholine copolymers, N-vinyl pyrrolidone - methyl methacrylate copolymers, methyl methacrylate - acryloyl morpholine copolymers, hydroxyethyl methacrylate - acryloyl morpholine copolymers, methoxyethyl methacrylate - ethoxyethyl methacrylate copolymers, and methoxy methacrylate - acryloyl morpholine copolymers.

5 Suitable desiccant polymers of the type comprising a polymeric matrix in which is dispersed a desiccant material are disclosed in WO 96/04189, the contents of which 10 are included herein by way of reference, an example of such a desiccant polymer being an elastomeric polymer, such as a rubber, compounded with a desiccant material.

15 Such a rubber may be a natural rubber, or a synthetic rubber such as a butadiene-based rubber, e.g. based on styrene-butadiene or cis-1,4-polybutadiene, butyl rubber, halobutyl rubber, ethylene-propylene rubber, neoprene, nitrile rubber, polyisoprene, silicone rubber, chlorosulphonated polyethylene or epichlorhydrin elastomer, or a mixture, blend or copolymer thereof. Halobutyl, e.g. chlorobutyl or bromobutyl rubbers and silicone rubbers are pharmaceutically acceptable rubbers known for use as materials for stoppers etc. As mentioned above to be maintained in contact with pharmaceutical products. Such rubbers are sufficiently permeable to water 20 vapour that the desiccant material compounded with the rubber can exert its desiccant effect through a layer of the material.

25 Such rubbers may be compounded in the manner with which they are conventionally compounded for manufacture, of rubber articles, as known in the art. For example they may be compounded with reinforcing fillers, colouring agents, preservatives, antioxidants, additives to modify their stiffness, chemical resistance etc. such as curing/vulcanising agents. Conventional reinforcing fillers include inorganic reinforcing fillers such as zinc oxide and silicas such as china clay and other clays. Suitable compounding processes and compositions will be apparent to those skilled in the art of compounding of rubbers.

30 In such a desiccating polymer of this last-mentioned type, the polymer includes particles of a solid desiccating material dispersed in its bulk. In rubbers a reinforcing filler, such as china clay, is normally compounded into the rubber, and in a desiccating rubber this filler may be totally or preferably partly replaced with the particles of solid desiccating material. Total replacement may lead to a loss of mechanical strength as 35 compared to a rubber using entirely china clay as its filler, although desiccants may be found which can be used as the entire filler without loss of strength. Such a powdered desiccating material may have a particle size the same as or similar to that of the conventional inorganic fillers referred to above, so that the desiccant can serve as the filler as well. The quantity of the powdered desiccating material used may be up to the

quantity in which conventional inorganic fillers are used, that is, they may completely replace the usual inorganic filler. For example the powdered desiccant may replace up to 50% of the weight of the normal weight of filler used in the rubber, e.g. 10-50%, such as 20-40%. The quantities of filler normally used in a rubber for a particular 5 application such as a vial stopper will be known to those skilled in the art.

The compounded rubber may also additionally include a conventional filler as mentioned above, for example in a quantity which together with the powdered desiccant comprises up to the weight % of filler normally included in such a rubber. The quantity of desiccant necessary for a particular product contained in the container 10 will depend upon the application but can easily be determined by experiment.

Particularly preferred desiccant materials are dried molecular sieves and calcium oxide, or mixtures thereof. Suitable inorganic desiccants are the known materials sold in the UK under the names Grace A3TM, SiliporiteTM and Ferben 200TM. Calcium oxide chemically fixes water by formation of calcium hydroxide, from which 15 water can only be released at extreme temperatures, and absorbed water can generally only be released from molecular sieves at several hundred °C, that is, well above the temperatures containers of pharmaceutical substances would be expected to experience under normal storage. When the desiccant is calcium oxide, although the process is not to be seen as bound by any specific chemical theory, the process is believed to remove 20 absorbed water before this reacts chemically with the calcium oxide.

A preferred elastomeric polymer is therefore a halobutyl, e.g. chlorobutyl or bromobutyl, rubber, which in the case of a desiccating rubber is compounded with an inorganic desiccant such as a molecular sieve or calcium oxide.

The process according to the second aspect of this invention appears to be 25 suitable for a range of polymers, e.g. rubbers of the above-mentioned type even without any compounded desiccant material, and plastics materials such as those commonly used for packaging, e.g. polyalkylenes such as polythene etc.

The polymer, whether a desiccating polymer of the first aspect of this invention, or a non-desiccating polymer of the second aspect, may be provided in any 30 solid shape for use in the process of this invention, for example three dimensional bodies, coatings, thin films. In particular the process is suitable for use with the above-described stoppers for vials. Generally there are two types of such stoppers; being those for general use with moisture sensitive pharmaceutical substances, and those 35 specifically intended for use with lyophilised substances, having a cut out in their lower part to enable the water of the solution containing the substance to be lyophilised to evaporate during the lyophilisation process. The process of this invention is suitable for use with all types of such stoppers.

Polymers which have their desiccating capacity enhanced by the process of the invention can be used for all purposes in which a polymer having a desiccating capacity

is required, e.g desiccating packaging, e.g for moisture sensitive pharmaceutical products.

Suitable electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules, generally causing the water molecules to be heated, includes 5 microwave radiation and RF radiation. Such radiation preferentially heats water molecules contained, e.g absorbed within a solid or semi-solid body, such as the elastomeric and desiccant polymers of the present invention. Electromagnetic radiation of this nature is well known in the art. Typically microwave radiation of the wavelength 1mm - 15cm (= frequency 3×10^{11} - 2×10^9 Hz) may be used, but radiation 10 of other wavelength/ frequency may be used. An example of such radiation is that having a frequency of nominally 2450 Mhz. Suitable generators for such radiation, and apparatus in which solid bodies made of the above described polymers may be exposed to such radiation will be known to those skilled in the art. In the process of this 15 invention the polymer may be exposed to a single wavelength, to two or more wavelengths or to a spectrum of wavelengths.

In practice the optimum objective is to achieve maximum removal of absorbed water and activation with minimum thermal damage to the polymer matrix, as manifested for example in surface stickiness after exposure to the microwave radiation. In practice the optimum wavelength/frequency, power level, exposure time, 20 distribution and loading of the exposure apparatus with the polymer, and other conditions of the process for any particular type of polymer, or solid body into which the polymer is made, can be determined by relatively easy experimentation.

In general it is preferred to use a lower microwave radiation power for a longer exposure time, rather than vice versa.

25 In some cases, when a number of solid bodies, e.g the vial stoppers referred to above, of the desiccant polymer are exposed to the microwave radiation, it is preferred to expose a smaller number of the bodies at a time. In some cases exposure of a larger load of such bodies can lead to greater water removal / activation, but greater surface stickiness.

30 When a number of solid bodies, e.g the vial stoppers referred to above, of the desiccant polymer are exposed to the microwave radiation it is preferred to distribute the bodies evenly.

The polymer may be exposed to the microwave radiation in a single cycle. Alternatively the polymer may be exposed to the microwave radiation in a pulsed 35 cycle, i.e exposure of the polymer to the microwave radiation for a, usually short, period, followed by a resting phase during which the polymer is not exposed to the radiation, followed if necessary by further alternating exposure and resting phases. In the case of the above described vial stoppers made of desiccant polymer, two exposure cycles separated by a resting cycle may be sufficient.

It is preferred to carry out the process of the invention on polymers, whether desiccant or otherwise, as soon after manufacture as possible to remove moisture from the polymer before the moisture has had time to permeate deeply into the bulk of the polymer. This is particularly so in the case of polymers which have a low permeability 5 to moisture, as it could consequently be difficult for the moisture to permeate out of the polymer during the process of the invention.

Various means will be apparent to those skilled in the art to carry out the process of the invention on an industrial scale, e.g to apply the process to a large 10 number of solid bodies of the desiccant polymer, e.g the vial stoppers referred to above, thin films, coatings etc. of the polymer. Such means may include automation of the process, large scale batch operation, rotating or tumbling the bodies whilst they are exposed to the microwave radiation to achieve all-round exposure, adaptation to continuous operation e.g using conveyor systems etc., use of multiple processing 15 systems or multiple microwave radiation generators etc. All such are encompassed within the generality of the present invention.

After polymers have been treated in the process of the invention it is preferred to store them in a container which is impermeable to atmospheric moisture, and which may itself be desiccated.

The invention will now be described by way of non-limiting example only, with 20 reference to the accompanying drawings, Figs. 1 - 8, which show graphs of moisture absorption isotherms for stoppers of various types exposed to microwave radiation and differentials between water uptake for stoppers activated by the process of this invention and non-activated stoppers.

25 **Example 1:**

Desiccant Polymer.

The desiccant polymer used was a brominated butyl rubber of a type widely used for the manufacture of pharmaceutical vial stoppers, compounded with 40 parts 30 per hundred rubber ("phr") of a standard talc filler and 40 phr of a molecular sieve desiccant, and other entirely standard ingredients. The particle size of the molecular sieve was similar to that of the talc, and the compounding of the desiccant rubber was by an entirely conventional process. The desiccant rubber was moulded into vial 35 stoppers (both conventional and lyophilisation) of an entirely conventional shape and size, being about 2cm top flange diameter and about 1cm (conventional) or 1.5 cm (lyophilisation) deep, weighing about 2g. The manufacturing process for the stoppers involved several water washes.

Control Polymer.

The control polymer used was in the form of a vial stopper of identical size and shape to the desiccant polymer stoppers, but made of a brominated butyl rubber of a type widely used for the manufacture of pharmaceutical vial stoppers, compounded with 80 parts per hundred rubber ('phr') of a standard talc filler and no desiccant.

5

Microwave Generator.

The microwave generator was a standard unmodified commercially available domestic Sanyo Super Showersave™ 800w model with six variable power settings selectable between 80 and 800w. The microwave output frequency was nominally 10 2450 Mhz.

Microwave Cycle Optimisation.

1) Designed experiment.

15 A full factorial, centered, designed experiment was run on a range of power outputs and turntable loading factors. Results were analysed using Designease™ software. The basic conclusions of the study were that:

20 There was a strong interrelation between power and exposure time for both water removal and surface stickiness of the stoppers. Lower power (e.g 80- 400 w) for longer time (e.g 5-10 minutes) gave better results for both, than for example a higher power of 1000 w for the shorter time of 30 seconds.

25 There was a relatively weak effect for numbers of stoppers per load of both water removal and stickiness. At greater load the water removal was higher, but so was stickiness. This effect was more marked at higher power.

30 Distribution of the load of stoppers seemed to have little effect, but optimum results were achieved with a uniform load.

Optimum results for greatest water removal with minimal adverse effect on the rubber characteristics were obtained at medium power (in this case 450w) for a moderate exposure time with a well distributed load of stoppers.

2) Pulsed exposure.

30 For all pulsed exposure studies 10 evenly distributed stoppers were used as a load. The pulse cycle was selected on the basis of conditions found to be tolerated by the stoppers, which were, for all powers up to and including 700w, repeated cycles of 5 minutes on followed by 2 minutes off, and for 800w 2 minutes on followed by 2 minutes off. In all cases the bulk of water removal was achieved in the first two cycles.

35 At the end of these two cycles there was no apparent adverse effect upon the rubber. Further heating cycles did lead to greater water removal but at the expense of eventual damage to the rubber. The amount of time needed to damage the rubber was directly proportional to the microwave power. At power levels of 450w and above, all conditions achieved similar maximum water removal, a weight loss of about 5mg per

stopper occurring (which may include loss of other volatiles as well as water) without damage to the rubber.

Optimum activation of the stoppers could be achieved with a pulsed cycle of 5 minutes on / 2 minutes off / 5 minutes on at 450w power, but a single cycle of 450 w for 5 minutes, or 600 w for 3 minutes, was almost as good. Water loss was around 3 mg per stopper.

Results.

10 Stoppers, both of conventional and lyophilisation mouldings, along with control stoppers, were either optimally activated by exposure to microwave radiation, using a pulsed cycle as described above, or used non-reactivated as received.

15 These stoppers were exposed to a controlled relative humidity atmosphere of either 11%RH or 75%RH at 25°C using saturated salt solutions for RH control. The stoppers were individually weighed at time intervals and the mean weight gain/loss plotted against time. The resulting graphs are attached as Figs 1-8, together with graphs showing the differential between activated and non-activated stoppers. These graphs clearly show that reactivating the stoppers:

- 1) Increases their initial rate of water pick-up.
- 2) Has a marked effect on moisture pick up at lower RH.
- 20 3) Has beneficial effects even upon the control stoppers, e.g imparting some desiccating capacity even to control stoppers, although in all cases the desiccant rubber stoppers showed markedly greater moisture uptake than control stoppers.
- 4) Removes at least 3.5 mg of water per stopper reproducibly.
- 5) Is not a pre-requisite for desiccant action by the desiccant rubber
- 25 stoppers. After 15-30 days the rate of moisture pick-up seems to be similar for both activated and non-activated stoppers, however the extent of moisture uptake is different since the non activated stoppers start from a lower base.
- 6) It is probable that the eventual absorbed water capacity of the activated stoppers will be higher than their non-activated counterparts.
- 30 It was noticed that lyophilisation stoppers take up more moisture than conventional stoppers. This is believed to be a consequence of the greater weight of desiccant rubber in lyophilisation stoppers.

Claims:

1. A process for the enhancement of the desiccating capacity of a desiccant polymer characterised in that it includes the step of exposing the said desiccant polymer to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules.
2. A process for enhancing the desiccating capacity of a polymer, or of imparting a desiccating capacity to a polymer characterised in that it includes the step of exposing the said polymer to electromagnetic radiation of a wavelength/frequency that is absorbed by water molecules.
3. A process according to claim 1 characterised in that the desiccant polymer is an inherently desiccant polymeric material.
4. A process according to claim 3 characterised in that the desiccant polymer is a hydrophilic polymer.
5. A process according to claim 4 characterised in that the hydrophilic polymer is a hydrogel polymer.
6. A process according to claim 1 characterised in that the desiccant polymer comprises a polymeric matrix in which is dispersed a desiccant material.
7. A process according to claim 6 characterised in that the desiccant polymer is a rubber compounded with a desiccant material.
8. A process according to claim 7 characterised in that the desiccant polymer is a halobutyl rubber, which is compounded with an inorganic desiccant selected from molecular sieve or calcium oxide.
9. A process according to claim 2 characterised in that the polymer is a rubber without any compounded desiccant material, or a plastics materials.
10. A process according to any one of claims 1 to 9 characterised in that the polymer is in the form of a stopper for a pharmaceutical vial.
11. A process according to any one of the preceding claims characterised in that the electromagnetic radiation is microwave radiation or RF radiation.

12. A process according to any one of the preceding claims characterised in that the polymer is exposed to the microwave radiation in a single cycle.

5 13. A process according to any one of the preceding claims characterised in that the polymer is exposed to the microwave radiation in a pulsed cycle.

14. A process according to claim 13 characterised in that the pulsed cycle comprises two exposure cycles separated by a resting cycle.

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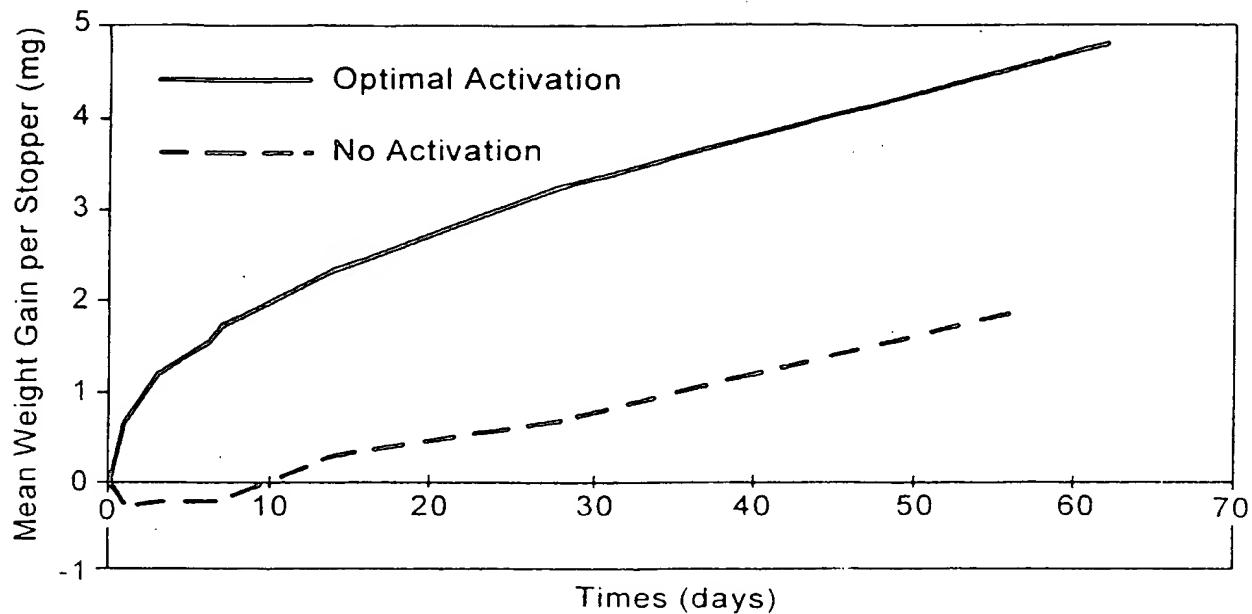


Fig. 1 Moisture Absorption Isotherm for Desiccant Stoppers,
Conventional Moulding - 11% r.h. Data

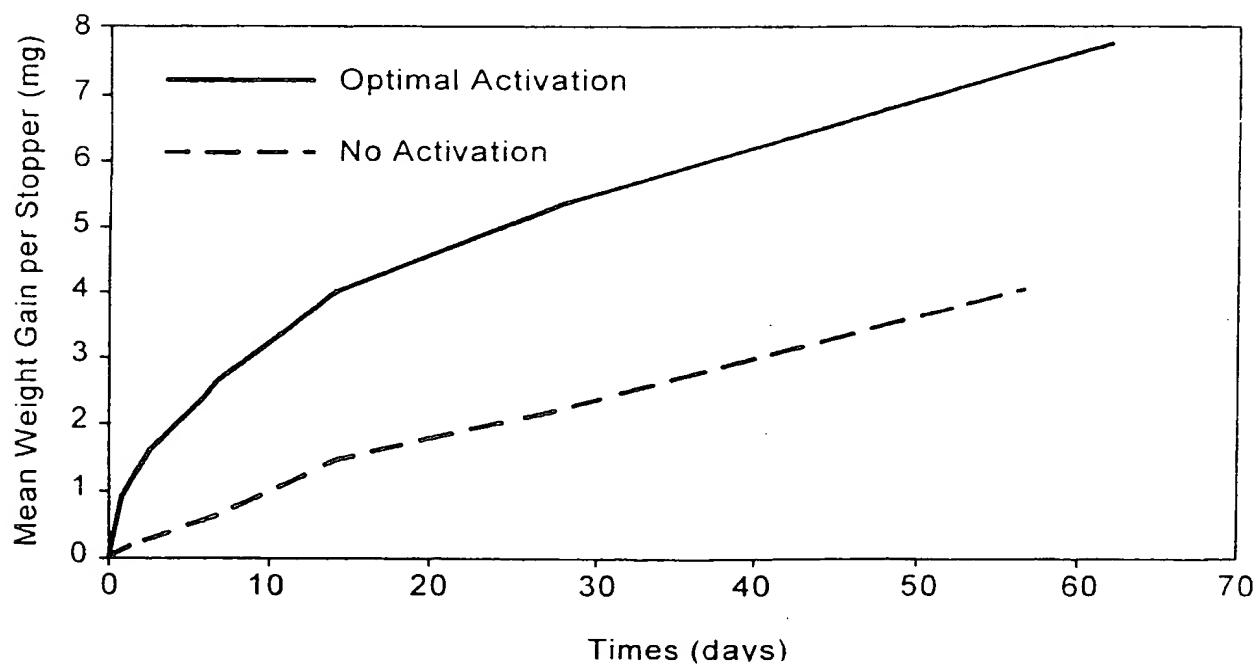


Fig. 2 Moisture Absorption Isotherm for Desiccant Stoppers,
Lyophilisation Moulding - 11% r.h. Data

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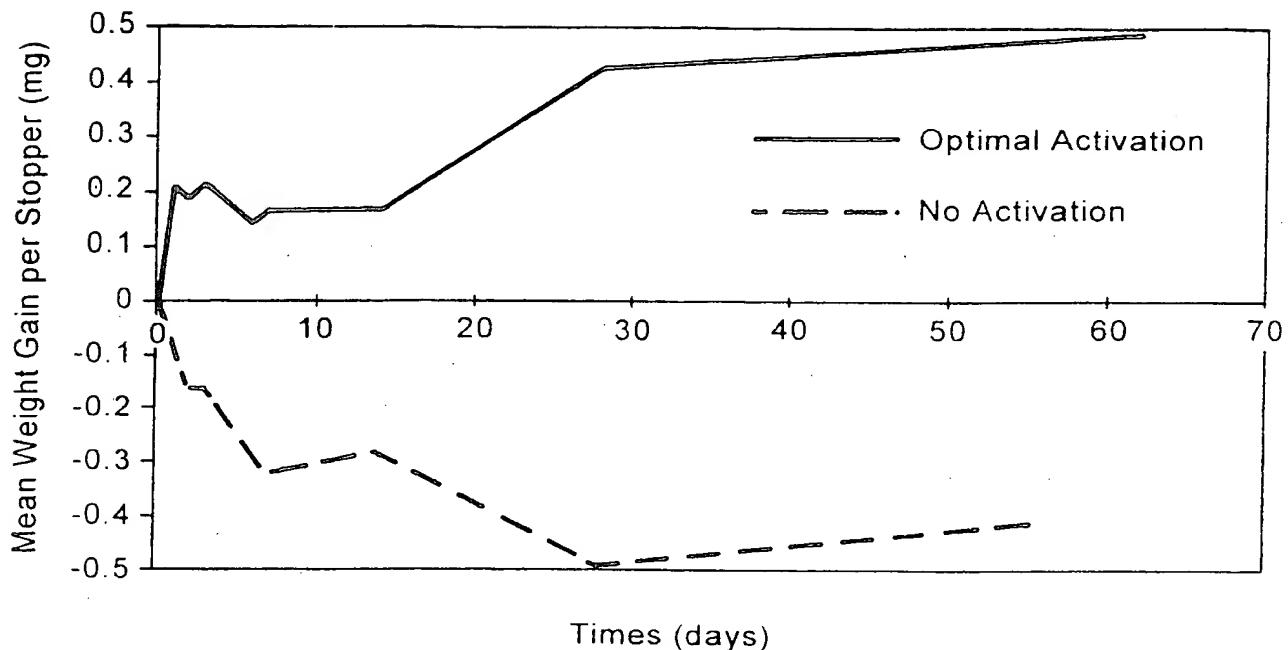


Fig. 3 Moisture Absorption Isotherm for Control Stoppers,
Conventional Moulding - 11% r.h. Data

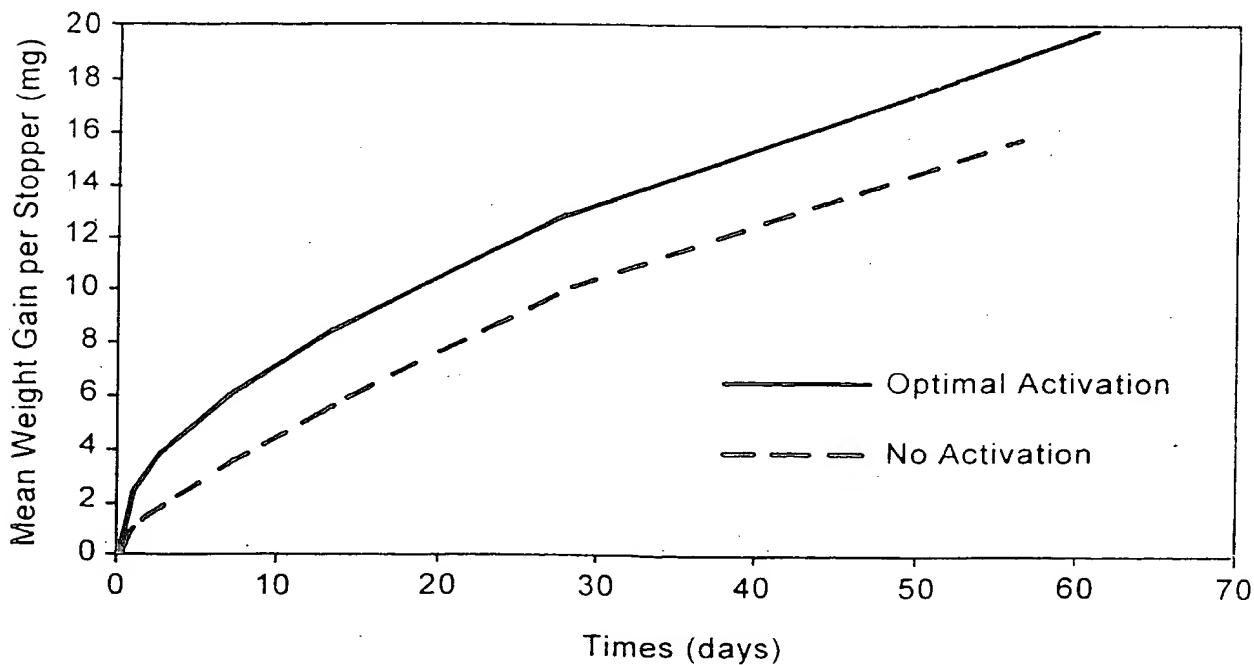


Fig. 4 Moisture Absorption Isotherm for Desiccant Stoppers,
Conventional Moulding - 75% r.h. Data

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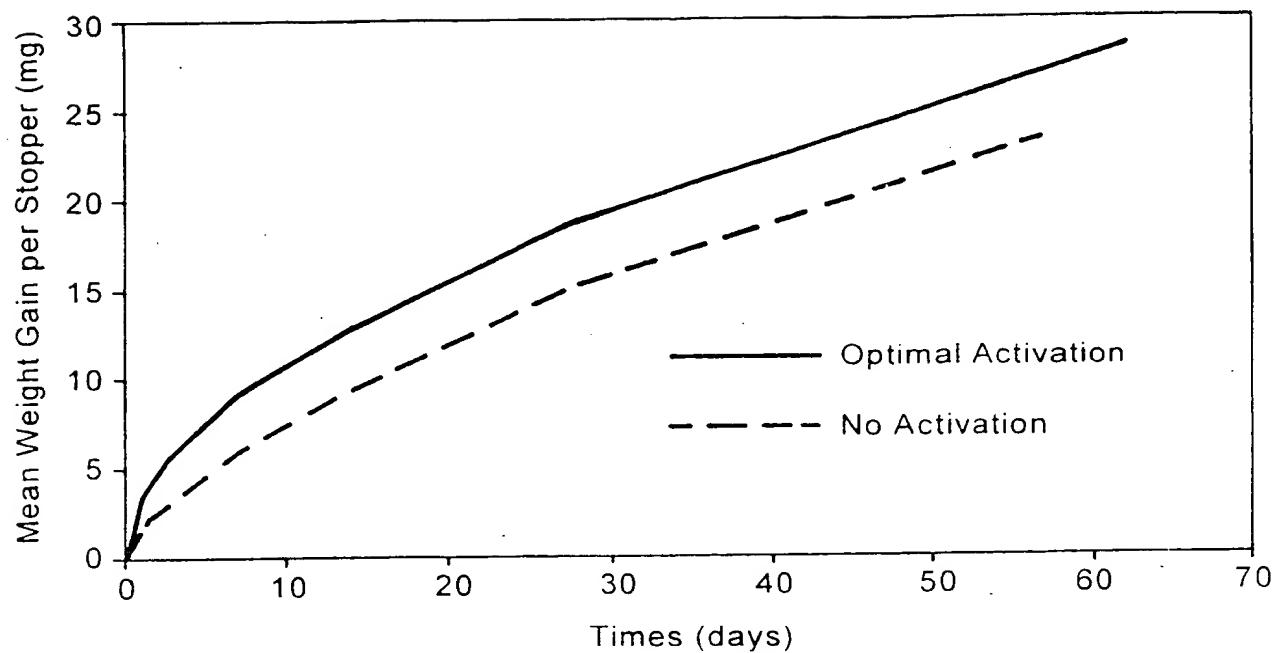


Fig. 5 Moisture Absorption Isotherm for Desiccant Stoppers,
Lyophilisation Moulding - 75% r.h. Data

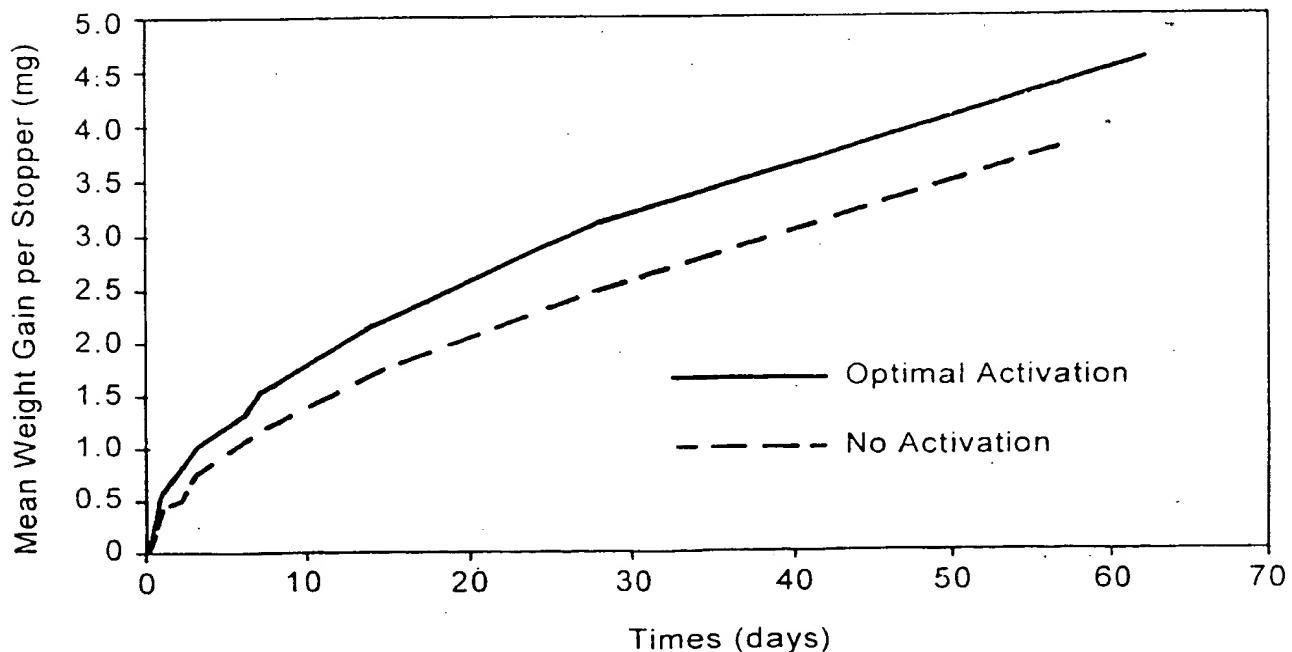


Fig. 6 Moisture Absorption Isotherm for Control Stoppers,
Conventional Moulding - 75% r.h. Data

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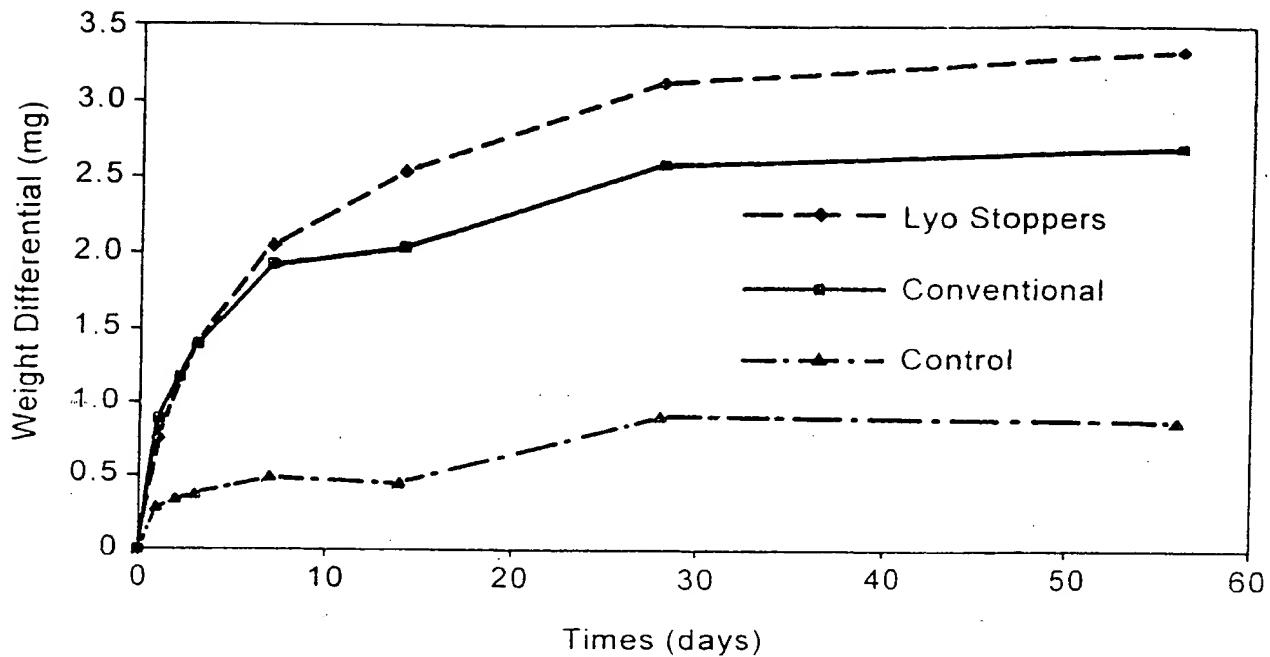


Fig. 7 Differential in Moisture Vapour Uptake Between Activated and Non Activated Stoppers - 11% Data

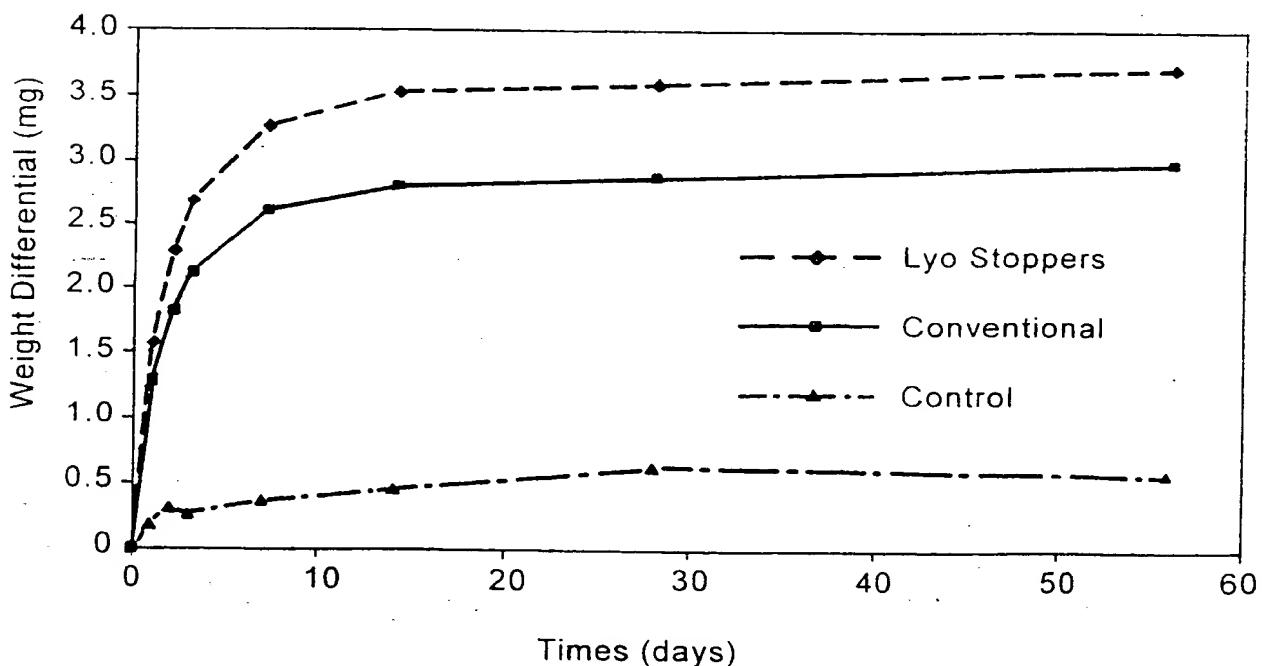


Fig. 8 Differential in Moisture Vapour Uptake Between Activated and Non Activated Stoppers - 75% Data

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02844

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08J/28

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08J B65D B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>DATABASE WPI Section Ch, Week 7513 Derwent Publications Ltd., London, GB: Class A14, AN 75-21559W XP002054232 & JP 49 083 729 A (MITSUBISHI RAYON CO LTD), 12 August 1974 see abstract</p> <p>---</p>	1-5.11
A	<p>DATABASE WPI Section Ch, Week 9519 Derwent Publications Ltd., London, GB: Class A17, AN 95-143994 XP002054233 & JP 07 068 125 A (MITSUI PETROCHEM IND CO LTD), 14 March 1995 see abstract</p> <p>---</p> <p>---</p>	1

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02844

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 04189 A (SMITHKLINE BEECHAM PLC ; TASKIS CHARLES BERNARD (GB); HOLLAND SIMON) 15 February 1996 cited in the application see claims 1-11 ---	1
A	US 4 805 317 A (INGLIS ROBERT S ET AL) 21 February 1989 see claim 1 ---	1
A	US 5 191 721 A (INCORVIA SAMUEL A ET AL) 9 March 1993 see claim 1 -----	1

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Information on patent family members

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